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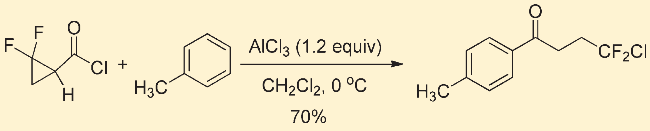
Friedel−Crafts Reactions of 2,2-Difluorocyclopropanecarbonyl Chloride: Unexpected Ring-Opening Chemistry

William R. Dolbier, Jr.,* Eric Cornett, Henry Martinez, and Wei Xu

Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, United States

Supporting Information



ABSTRACT: The Friedel−Crafts reactions of 2,2-difluorocyclopropanecarbonyl chloride with various arenes did not lead to the straightforward formation of the expected aryl 2,2-difluorocyclopropyl ketones. Instead the reactions proceeded, to various degrees depending on the reactivity of the arene, via an apparent rearrangement of the initially formed acylium ion to form novel aryl 3-chloro-3,3-difluoropropyl ketones. The ring-opened product was formed exclusively, and therefore the reaction may be synthetically useful when relatively unreactive arene substrates such as benzene, toluene, and *p*-xylene are used. No conditions were found where ring-intact products could be formed exclusively when using substituted benzenes as substrates, with the very reactive substrate thiophene being most selective in that regard, favoring ring intact product **3** with a selectivity of 98:2. The regioselectivity of ring-opening was examined and compared with other related systems computationally.

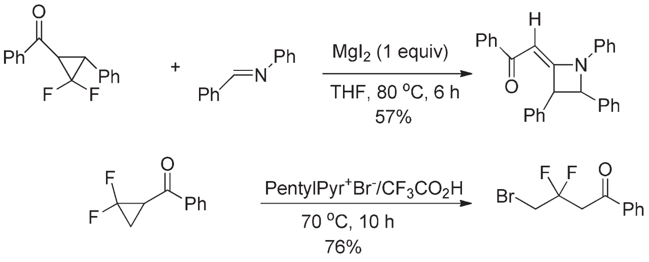
INTRODUCTION

The chemistry of 2,2-difluorocyclopropyl ketones has become an area of recent interest to us as a consequence of our discovery of difluorocarbene reagent TFDA (trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate), which facilitated their synthesis.[1] Two studies of reactions of 2,2-difluorocyclopropyl ketones that resulted in ring-opening were recently published. One was our study of the MgI_2-facilitated reactions of aryl 2,2-difluorocyclopropyl ketones with imines,[2] which led to products completely devoid of fluorine, and the second was of their ionic-liquid facilitated ring-opening by HBr. Examples of each of these reactions are given in Scheme 1.[3]

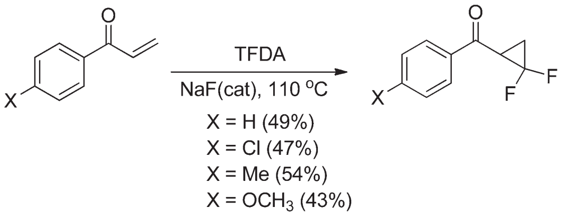
Unfortunately, use of TFDA for the synthesis of unsubstituted aryl difluorocyclopropyl ketones led only to moderate yields,[3] probably due to competing polymerization of their α,β-unsaturated ketone precursors (Scheme 2). Therefore an alternative synthesis of the 2,2-difluorocyclopropyl ketones, which involving Friedel−Crafts acylation of activated aromatics using 2,2-difluorocyclopropanecarbonyl chloride, **1**, was considered. There were a number of published examples of successful use of the *nonfluorine*-containing cyclopropanecarbonyl chlorides in Friedel−Crafts acylations,[4] including those shown in Scheme 3.[5]

Since the dichloro analogue 2,2-dichlorocyclopropanecarbonyl chloride had been used effectively under the usual acylation conditions,[6] there was good reason to believe that use of 2,2-difluorocyclopropanecarbonyl chloride would lead to similar success.

Scheme 1. Recent Studies of the Ring-Opening Chemistry of Aryl 2,2-Difluorocyclopropyl Ketones



Scheme 2. TFDA-Facilitated Synthesis of Aryl 2,2-Difluorocyclopropyl Ketones



RESULTS

2,2-Difluorocyclopropanecarbonyl chloride (**1**) was prepared from *n*-butyl 2,2-difluorocyclopropanecarboxylate via base-catalyzed hydrolysis followed by reaction of the carboxylic acid with thionyl chloride. When **1** was allowed to react with $AlCl_3$ in the presence of 1 equiv of benzene in CH_2Cl_2 at 0 °C, surprisingly *none* of the expected aryl 2,2-difluorocyclopropyl ketone was obtained. Instead, only the ring-opened product **2a** was obtained,

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in 50% yield. Compounds of this structure, that is aryl 3-chloro-3,3-difluorocyclopropyl ketones, have, to our knowledge, not been previously reported; so this reaction has potential synthetic importance.

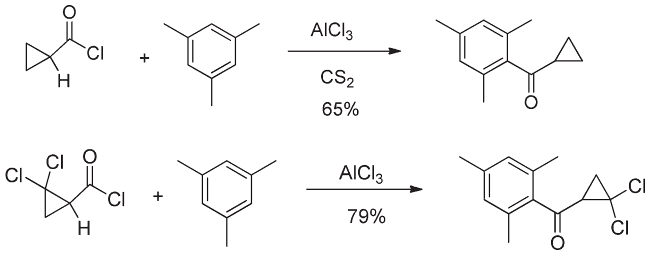
When toluene, ethylbenzene, or *p*-xylene were used as the aromatic substrate, analogous ring-opened products (**2b**, **2c**, and **2d**) were again the only products observed, this time in 70%, 78%, and 78% yields, respectively (Scheme 4). Toluene and ethylbenzene gave only the para-products, no ortho-products being observed. That the ortho position was considerably less reactive than the para was demonstrated by a competition experiment between toluene and *p*-xylene. When the reaction was carried out with equal amounts of each substrate, the only product obtained (**2b**) derived from reaction with toluene.

When the highly activated anisole was used as substrate, now the major product (75%) was **3e**, which retained the 2,2-difluorocyclopropane entity, along with 25% of ring-opened product **2e** (Scheme 5). The very electron-rich heterocycle thiophene was an excellent substrate, yielding 86% of a mixture of mostly (98:2) ring-intact product **3f**.

When instead of 1 equiv of aromatic substrate 5 equiv were used in the reactions, some ring-intact product **3a** (20%) was observed for benzene, and for toluene the ring-intact **3b** was now the major product (90%). Xylene still yielded only ring-opened product **2d**. Overall yields of the reactions were not much affected by the change from 1 to 5 equiv of aromatic substrate, nor could this change lead to *exclusive* formation of the desired ring-intact products **3** for any of the benzene derivatives. The results from all of these reactions are summarized in Table 1.

Methylene chloride was in retrospect fortuitously chosen as the solvent for these Friedel–Crafts reactions of acyl chloride **1** in our initial experiments. Other, perhaps equally traditional solvents for Friedel–Crafts reactions were later examined, and somewhat surprisingly, neither carbon disulfide nor nitrobenzene proved satisfactory as solvents. No acylation products were obtained when using either solvent. On the other hand, 1,2-dichloroethane proved to be an excellent solvent for the reaction, providing higher overall yields, while giving considerably more unrearranged, ring-intact products (**3**) than the analogous reactions in methylene chloride (Scheme 6). It is not clear why this is so. Mixtures of $AlCl_3$ with both ethylene dichloride and CH_2Cl_2 (in the absence of **1**) slowly darken, with methylene chloride

Scheme 3. Examples of Friedel–Crafts Acylation with Cyclopropanecarbonyl Chlorides



Scheme 4. Initial Friedel–Crafts Reactions of 1

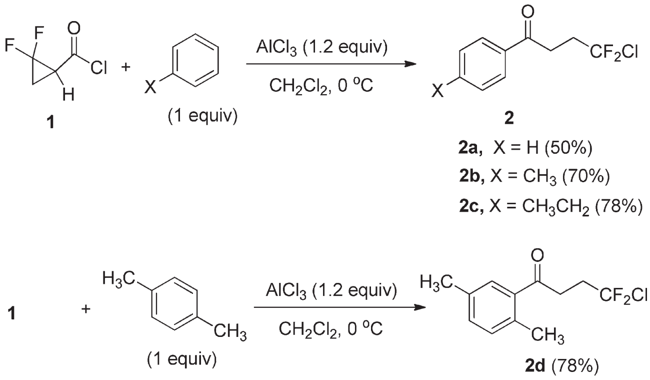
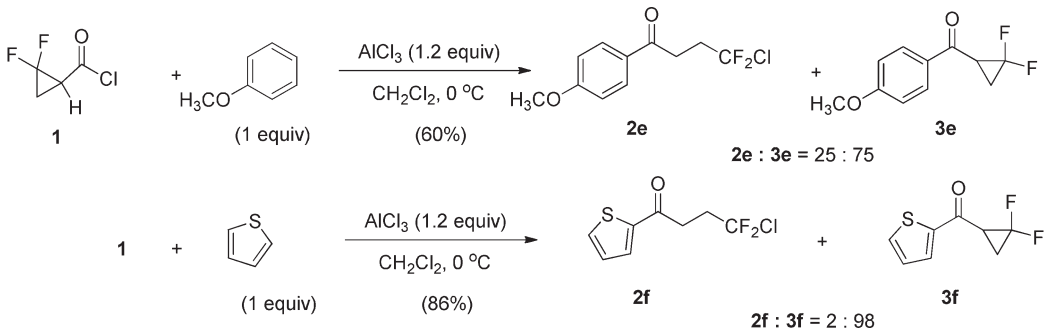


Table 1. Friedel–Crafts Reactions of Aromatics with 2,2-Difluorocyclopropanecarbonyl Chloride in Methylene Chloride[a]

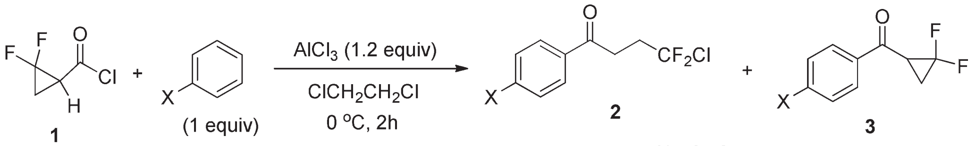
			ratio of products	
substrate	equiv of substrate	overall yield (%)	2	3
benzene	1	50	**2a**: 100	**3a**: 0
benzene	5	55	**2a**: 80	**3a**: 20
toluene	1	72	**2b**: 100	**3b**: 0
toluene	5	70	**2b**: 10	**3b**: 90
ethylbenzene	1	78	**2c**: 100	**3c**: 0
p-xylene	1	78	**2d**: 100	**3d**: 0
p-xylene	5	75	**2d**: 100	**3d**: 0
anisole	1	52	**2e**: 25	**3e**: 75
anisole	5	60	**2e**: 12	**3e**: 88
thiophene	1	86	**2f**: 2	**3f**: 98

[a] Unless otherwise specified, all reactions were carried out with 6 mmol of **1**, 7.2 mmol of $AlCl_3$ in 20 mL of CH_2Cl_2 at 0 °C for 2 h.

Scheme 5. Friedel–Crafts Reaction of 1 with Anisole and Thiophene



Scheme 6. Use of 1,2-Dichloroethane As Solvent for Friedel−Crafts Acylations of 1

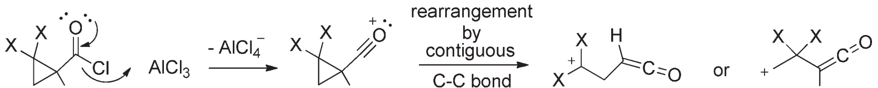


X = H (50%), **2a**:**3a** = 65:35

X = CH$_3$ (74%), **2b**:**3b** = 22:78

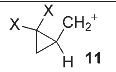
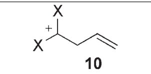
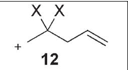
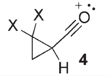
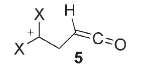
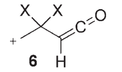
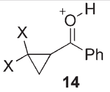
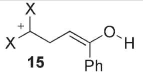
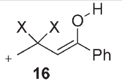
X = OCH$_3$ (72%), **2e**:**3e** = 10:90

Scheme 7. Relative Energies of Cyclopropyl Acylium Ions versus Their Respective Ring-Opened Ketene Carbocations (in kcal/mol), As Calculated by the ab Initio HF Method, in CH$_2$Cl$_2$ Environment

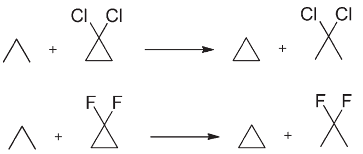


4		**5**	**6**
[0]	**4**$_F$, X = F	**+10.4**	+40.9
[0]	**4**$_{Cl}$, X = Cl	+17.3	+44.8
[0]	**4**$_H$, X = H	+40.9	+49.7

Table 2. Computed Ground States of Cyclopropane-Substituted Carbocations and Their Respective Ring-Opened Cations (ab initio HF and MP2/6-31G(d)) (kcal/mol)

Cyclopropyl-methyl cation		 **11**		 **10**		 **12**	
X	Solvent?	HF	MP2	HF	MP2	HF	MP2
X = H	no	[0]	[0]	+21.6	+30.6	+21.6	+30.6
	yes	[0]	[0]	+17.2	+24.5	+17.2	+24.5
X = F	no	[0]	[0]	+1.2	+3.6	+40.6	+53.1
	yes	[0]	[0]	**- 12.4**	+0.5	+25.8	+49.5
Cyclopropyl-acylium ion		 **4**		 **5**		 **6**	
X = H	no	[0]	[0]	+45.1	+55.0	+45.1	+55.0
	yes	[0]	[0]	+40.9	+52.6	+40.9	+52.6
X = Cl	no	[0]	[0]	+16.2	+19.9	+38.0	+39.2
	yes	[0]	[0]	+17.3	+20.9	+44.8	+47.7
X = F	no	[0]	[0]	+12.4	+19.8	+52.0	+61.8
	yes	[0]	[0]	**+10.4**	+18.2	+49.7	+59.4
Protonated cyclopropyl ketone		 **14**		 **15**		 **16**	
X = H	no	[0]	[0]	+43.2	+54.6	+43.2	+54.6
	yes	[0]	[0]	+38.0	+48.8	+38.0	+48.8
X = F	no	[0]	[0]	+20.9	+24.0	+55.0	+61.2
	yes	[0]	[0]	**+15.6**	+17.9	+48.8	+56.2

Scheme 8. Isodesmic Equations Describing the Effect of Geminal Fluorine and Chlorine Substituents on Cyclopropane Ring Strain (kcal/mol)



	HF/6-31g(d)	MP2/6-31g(d)
Cl, Cl	-4.42	-5.51
F, F	-12.37	-13.29

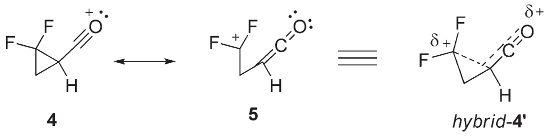


Figure 1. Hybrid structure for difluoro acylium ion **4**.

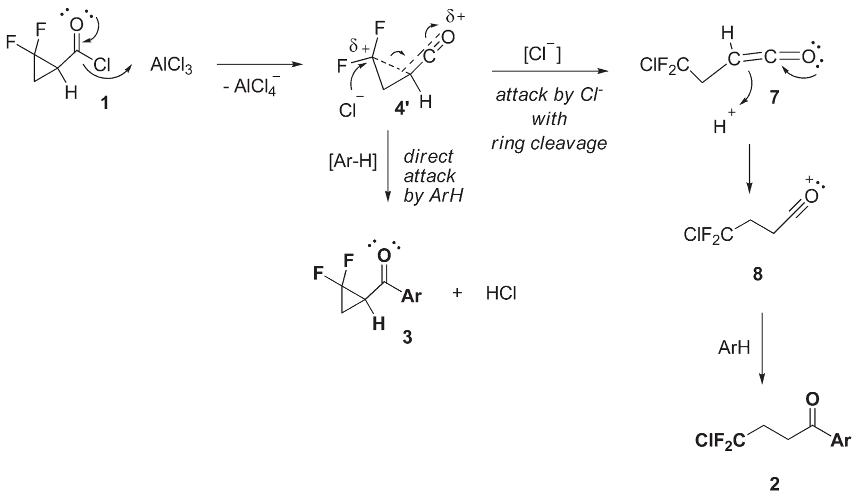
appearing to be less stable. Thus the exact nature of the catalyst may vary somewhat for the two solvents. Neither reaction is totally homogeneous.

■ DISCUSSION

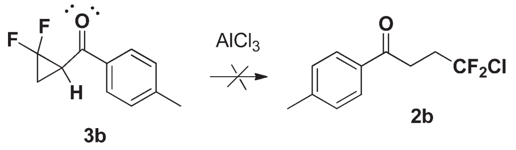
As indicated above, these results were unexpected because precedent of Friedel−Crafts reactions with both the unsubstituted and the 2,2-dichlorocyclopropanecarbonyl chlorides gave no evidence of rearrangement to analogous ring-opened products.[4−6] Why should the 2,2-difluorocyclopropyl system behave differently? Most likely the results reflect the difference in the thermodynamics of the hypothetical rearrangements of the respective acylium ion intermediates (**4**). Insight into this issue was gained through computation.

The ground states of a series of cyclopropane-substituted carbocations and their respective ring-opened cations were calculated in the gas phase at HF and MP2/6-31G(d) levels of theory using the Gaussian 03 Revision E01 package.[7] The stability provided by the solvent (dichloromethane) was also considered and calculated by using the Onsager model for both HF and MP2 methods. The results of these calculations are given in Table 2.

Scheme 9. Proposed Mechanism for Competitive Formation of 2 and 3



Scheme 10. Attempted $AlCl_3$-Catalyzed Rearrangement of 2,2-Difluorocyclopropyl Ketone



Scheme 7 summarizes the HF computational data for the solvated 2,2-difluoro-, 2,2-dichloro-, and unsubstituted-cyclopropyl acylium ions (4_F, 4_{Cl}, and 4_H) and their respective possible rearranged carbocations (5 and 6). The calculations indicate that in each case, the acylium ions 4 were more stable than either of the ketene carbocations 5 and 6 that could have been obtained from rearrangement. In both the fluorine- and the chlorine-substituted systems, cations 6_F and 6_{Cl} were substantially less stable than 5_F and 5_{Cl}, respectively, because of the detrimental inductive effects of the β-halogen substituents. Fluorinated carbocation 5_F is more stable than chlorinated analogue 5_{Cl} for two reasons. First, α-fluorines stabilize carbocations whereas α-chlorines do not, and second because there is a larger release of cyclopropane strain in the fluorinated case. The substantial (~12−13 kcal/mol) impact of geminal fluorines on the strain of cyclopropanes has long been recognized and its magnitude confirmed experimentally[8] and computationally.[9] However, to our knowledge, there is no comparable information available on the thermodynamic effect of geminal chlorines. Thus we provide the appropriate isodesmic equation for chlorine in Scheme 8, the value calculated by using the same method used by Wiberg in his computational study of fluorinated cyclopropanes.[9] Our corroborative calculation for the fluorine system is also included. These calculations confirm that geminal chlorines do in fact increase the strain of cyclopropane, but much less so than geminal fluorine substituents.

Thus ketene carbocation 5_F, with fluorines at the cationic carbon, is considerably more stable (relative to the acylium ion) than either the chlorine-substituted or the unsubstituted, ring-opened carbocations, 5_{Cl} or 5_H. Therefore it would not be unreasonable to consider the actual "intermediate" in the difluoro case to be best represented as a resonance hybrid (4′) of structures 4 and 5, as depicted in Figure 1, with the CF_2 carbon bearing significant + charge (much more so than the CH_2 group). The situation therefore might well behave much like a "bromonium" ion does, and undergo direct displacement at that carbon, which has the weaker C−C bond, that is at the CF_2 carbon.

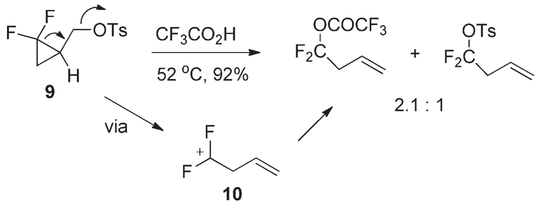
With this in mind, the trend shown in Table 1 for rearranged versus rearranged products for the various arene substrates can nicely be explained by a mechanism in which attack of *hybrid* acylium ion **4′** by chloride ion competes with its direct acylation reaction with arene, the former process leading to rearranged products (**2**) and the latter to unrearranged products (**3**). This mechanism is depicted in Scheme 9. Consistent with this mechanism is the fact that the most reactive arene substrates, that is, anisole and thiophene, are the ones whose direct reactions with acylium ion **4′** compete effectively with chloride attack of **4′**. Strongly indicative are the experiments with five times the amount of benzene and toluene, which now yielded nonrearranged, ring-intact products. Both of these observations are consistent with the competitive mechanism proposed in Scheme 9.

Of course, there is also the possibility that the unrearranged products **3** might have rearranged to **2** under the reaction conditions. However, this possibility was ruled out by two experiments. First, allowing the reactions to run for twice as long did not lead to increased amount of rearranged products. Second, an experiment in which 2,2-difluorocyclopropyl ketone **3b** was stirred in CH_2Cl_2 at 0 °C with $AlCl_3$ for 2 h, led to no conversion to **2b**; indeed no reaction at all was observed (Scheme 10).

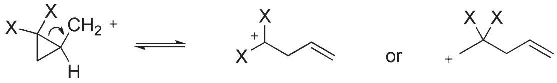
The regiochemistry of the nucleophile-induced ring-opening of acylium ion **4′** is consistent with that which was observed in our recent study of the solvolysis of 2,2-difluorocyclopropylmethyl tosylate (**9**) (Scheme 11),[10] which also resulted *only* in formation of products derived from the hypothetical ring-opened difluoromethyl carbocation **10**. A computational examination of this cyclopropylmethyl cation system, with and without fluorines, indicates that, in this case, difluoro ring-opened cation **10**, in a solvated environment, is actually more stable, by 12 kcal, than its respective ring-closed cation **11** (Scheme 12).

In stark contrast, the regiochemistry of the above two reactions is different from that observed by us in our study of the mechanistically similar HBr-induced ring-opening of aryl 2,2-difluorocyclopropyl ketones (shown above in Scheme 1).[3] In a

Scheme 11. Solvolysis of 2,2-Difluorocyclopropylmethyl Tosylate

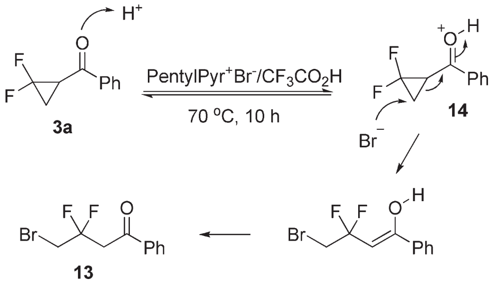


Scheme 12. Relative Energies of Cyclopropylmethyl Cations versus Their Respective Ring-Opened Allylcarbinyl Carbocations (in kcal/mol), As Calculated by the ab Initio HF Method, in CH_2Cl_2 Environment



	11	10	12
X = H	[0]	+17.2	+17.2
X = F	[0]	**- 12.4**	+25.8

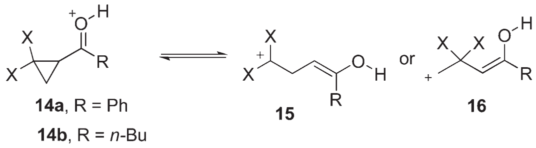
Scheme 13. S_N2-like Mechanism for HBr-Induced Ring-Opening of Ketone 3a



typical reaction of this type, when phenyl 2,2-difluorocyclopropyl ketone, **3a**, was allowed to react with HBr in an ionic liquid based reaction medium, the reaction resulted in the exclusive formation of 4-bromo-3,3-difluoro-1-phenylbutan-1-one, **13**, not the 4-bromo-4,4-difluoro product analogous to **2a** (Scheme 13). In this paper, the regiochemical outcome was rationalized on the basis of an S_N2-like mechanism, where bromide ion preferentially attacked at the more reactive CH_2 carbon of the cyclopropane ring, a mechanism that is remarkably similar to that proposed in Scheme 7 for the chloride-induced ring-opening of acylium ion **4**′, but which results in an *entirely different* regiochemical outcome! How can one rationalize the observed difference in regiochemical outcome for these two very similar reactions?

Again, one turns to theory for a possible answer. Calculating the relative energies of the protonated ketone intermediates, **14a**, fluorinated and nonfluorinated, and the two respective ring-opened enol carbocations, **15a** and **16a**, led to predicted more endothermic energetics for the hypothetical ring-opening of protonated ketone **14a** than for the acylium cation **4** (Scheme 14). This would be consistent with a more S_N2-like process for **14a**

Scheme 14. Relative Energies of Protonated Phenyl and *n*-Butyl Cyclopropyl Ketones versus Their Respective Ring-Opened Enol Carbocations (in kcal/mol), As Calculated by the ab Initio HF Method, in CH_2Cl_2 Environment



R = Ph, X = H	[0]	+38.0	+38.0
R = Ph, X = F	[0]	**+15.6**	+48.8
R = *n*-Bu, X = H	[0]	+36.6	+36.6
R = *n*-Bu, X = F	[0]	**+12.4**	+45.5

than for the acylium ion **4**, which is consistent with the results, although admittedly, it is difficult to argue that the difference between +15.6 and +10.4 kcal/mol (**15**$_F$ compared to **5**$_F$) would be sufficient in and of itself to explain a complete switch in regiochemistry for the two reactions.

Another factor can also be contributing significantly to the different regiochemical outcomes. Bromide ion is a much better nucleophile than chloride ion, and therefore bromide would be a more "aggressive" nucleophile in an S_N2 reaction than would chloride ion. Thus, all other things being equal, bromide ion would be more likely than chloride ion to take advantage of the greater S_N2 reactivity of the CH_2 group of protonated ketone **14a**. The observed regiochemical dichotomy can be compared with the notoriously variable regiochemical behavior of unsymmetrical epoxides in their ring-opening reactions with nucleophiles depending on choice of nucleophile and/or choice of Lewis or protic acid.

■ CONCLUSIONS

In conclusion, the Friedel–Crafts reactions of 2,2-difluorocyclopropanecarbonyl chloride (**1**) with various arenes did not lead to the straightforward formation of the expected aryl 2,2-difluorocyclopropyl ketones (**3**). Instead the reactions proceeded, to various degrees depending on the reactivity of the arene, via an apparent rearrangement of the initially formed acylium ion to form novel aryl 3-chloro-3,3-difluoropropyl ketones (**2**). The formation of the ring-opened product **2** was exclusive, and therefore could be synthetically useful, when relatively unreactive arene substrates such as benzene, toluene, and *p*-xylene are used, and when the reactions are run under dilute conditions with only 1 equiv of arene being used. No conditions were found where ring-intact products could be formed exclusively when using substituted benzenes as substrates, with the very reactive substrate thiophene being most selective in that regard, favoring ring intact product **3** with a selectivity of 98:2.

■ EXPERIMENTAL SECTION

Materials and Methods. Unless otherwise specified, proton, fluorine, and carbon NMR spectra were obtained in $CDCl_3$ at 300, 282, and 75.46 MHz, respectively, and chemical shifts are reported in ppm upfield relative to TMS for proton and carbon, and upfield of fluorotrichloromethane for fluorine. All aryl 2,2-difluorocyclopropyl ketones obtained and discussed in this work have been previously reported and characterized.[3]

Experimental Procedures

Preparation of 2,2-difluorocyclopropanecarbonyl Chloride (1)[11]

2,2-Difluorocyclopropanecarboxylic acid:[12] Potassium hydroxide (18.4 g, 3 equiv) was dissolved in 93 mL of water. *n*-Butyl 2,2-difluorocyclopropanecarboxylate (19.5 g, 1 equiv)[13] was added to the solution and the mixture heated to reflux and stirred for 10 h. The solution was cooled to room temperature, after which the volatiles were removed by rotary evaporation. Water was added to the crude solid dropwise until it dissolved. Concentrated hydrochloric acid was added dropwise until the solution reached a pH of 2. The acidic solution then was extracted with diethyl ether, after which the diethyl ether layer was then dried with anhydrous $MgSO_4$ and filtered, and the ether solvent was removed via rotary evaporation to provide 2,2-difluorocyclopropanecarboxylic acid as a pale yellow solid (9.4 g, 70%).[12] The acid was used without further purification in the next step.

2,2-Difluorocyclopropanecarbonyl chloride (1):[11] 2,2-Difluorocyclopropanecarboxylic acid (9.0 g) was dissolved in 75 mL of thionyl chloride under nitrogen. The solution was then heated to 60 °C and stirred for 6 h, after which the crude reaction mixture was distilled at atmospheric pressure to provide 2,2-difluorocyclopropanecarbonyl chloride **1** as a transparent, colorless liquid (9.3 g, 90%): bp 106–107 °C;[11] ^{1}H NMR δ 1.98 (m, 1H), 2.27 (m, 1H), 3.02 (m, 1H); ^{19}F NMR δ −124.6 (dm, *J* = 149 Hz, 1F), −138.3 (dm, *J* = 149 Hz, 1F).

Typical Procedure for Friedel–Crafts Reactions of 2,2-Difluorocyclopropanecarbonyl Chloride (1). Under nitrogen, appropriate (1 or 5) equivalents of the aromatic compound were added via syringe to 20 mL of anhydrous CH_2Cl_2 at 0 °C.2,2-Difluorocyclopropanecarbonyl chloride (**1**) (0.5 mL, 0.84 g, 1 equiv) was added to the solution at 0 °C followed by slow addition of 0.956 g (1.2 equiv) of $AlCl_3$. The mixture was then stirred under N_2 for 2 h at 0 °C. Then, water was slowly added to the mixture until two distinct layers formed and bubbling ceased. The entire solution was added to $NaHCO_3$ solution and the products were extracted with CH_2Cl_2. The CH_2Cl_2 layer was then dried with anhydrous $MgSO_4$, filtered, and then removed via rotary evaporation under reduced pressure, leaving behind a liquid crude mixture of aromatic compound plus product. Relative amounts of products **2** and **3** were determined by ^{19}F NMR analysis of the crude product mixture. Isolation of pure products was accomplished by column chromatography, using silica gel with hexane as eluent.

4-Chloro-1-phenyl-4,4-difluorobutan-1-one (2a): solid, 54%, mp 37–38 °C; ^{1}H NMR δ 2.79 (m, 2H), 3.30 (t, *J* = 7.2 Hz, 2H), 7.47 (m, 2H), 7.59 (m, 1H), 7.97 (d, *J* = 8.1 Hz, 2H); ^{19}F NMR δ −51.4 (t, *J* = 12.4 Hz, 2F); ^{13}C NMR δ 32.7 (t, J_{FC} = 2.6 Hz), 36.5 (J_{FC} = 25.2 Hz), 128.3, 129.0, 130.0 (J_{FC} = 291 Hz), 133.8, 136.4, 196.5; HRMS (EI) calcd for $C_{10}H_9OF_2Cl$ $[M + H]^+$ 218.0304, found 218.0305. Anal. Calcd for $C_{10}H_9OF_2Cl$: C, 54.94; H, 4.15. Found: C, 55.01; H, 4.08.

(2,2-Difluorocyclopropyl)(phenyl)methanone (3a):[3] liquid, obtained in 11% yield when using 5 equiv of benzene; ^{1}H NMR δ 1.80 (m, 1H), 2.42 (m, 1H), 3,38 (m, 1H), 7.46 (m, 2H), 7.60 (m, 1H), 8.02 (m, 2H); ^{19}F NMR δ −124.72 (m, 1F), −140.58 (m, 1F).

4-Chloro-1-(4-methylphenyl)-4,4-difluorobutan-1-one (2b): solid, mp, 61–63.5 °C, 72% and 7% yield, respectively, when using 1 or 5 equiv of toluene; ^{1}H NMR δ 2.43 (s, 3H), 2.79 (m, 2H), 3.29 (m, 2H), 7.28 (m, 2H), 7.88 (m, 2H); ^{19}F NMR δ −51.4 (t, *J* = 12.4 Hz, 2F); ^{13}C NMR δ 21.91, 32.6 (t, J_{FC} = 3.0 Hz), 36.6 (t, J_{FC} = 24.7 Hz), 129.4, 129.7, 129.97 (t, J_{FC} = 291 Hz), 133.9, 144.7, 196.2; HRMS (EI) calcd for $C_{11}H_{11}OF_2Cl$ $[M + H]^+$ 233.0539, found 233.0387. Anal. Calcd for $C_{11}H_{11}OF_2Cl$: C, 56.79; H, 4.77. Found: C, 56.88; H, 4.68.

(2,2-Difluorocyclopropyl)(4-methylphenyl)methanone (3b):[3] solid, mp 37–38 °C, 63% yield when using 5 equiv of toluene; ^{1}H NMR δ 1.75 (m, 1H), 2.39 (m, 1H), 2.40 (s, 3H), 3.35 (m, 1H), 7.49 (m, 2H), 7.66 (m, 2H); ^{19}F NMR δ −124.70 (m, 1F), −140.70 (m, 1F).

4-Chloro-1-(4-ethylphenyl)-4,4-difluorobutan-1-one (2c): liquid, 78%, bp 132 °C/10 mmHg; ^{1}H NMR δ 1.27 (t, *J* = 7.8 Hz, 3H), 2.68–2.86 (m, 4H), 3.29 (t, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 1H); ^{19}F NMR δ −51.45 (t, *J* = 12.4 Hz, 2F); ^{13}C NMR δ 15.3, 29.1, 32.6, 36.5 (t, *J* = 25.0 Hz), 128.4, 129.9 (t, *J* = 291 Hz), 133.8, 134.1, 150.8, 196.2; HRMS (EI) calcd for $C_{12}H_{13}OF_2Cl$ $[M]^+$ 246.0623, found 246.0604. Anal. Calcd for $C_{12}H_{13}OF_2Cl$: C, 58.43; H, 5.31. Found: C, 58.08; H, 5.28.

4-Chloro-1-(2,5-dimethylphenyl)-4,4-difluorobutan-1-one (2d): liquid, bp 91 °C/10 mmHg, 78% and 75%, respectively, when using 1 or 5 equiv of *p*-xylene; ^{1}H NMR δ 2.38 (s, 3H), 2.46 (s, 3H), 2.77 (m, 2H), 3.23 (t, *J* = 7.5 Hz, 2H), 7.20 (m, 2H), 7.48 (br s, 1H); ^{19}F NMR δ −51.43 (t, *J* = 12.4 Hz, 2F); ^{13}C NMR δ 21.0, 21.1, 35.1 (t, *J* = 2.5 Hz), 36.6 (t, *J* = 25.4 Hz), 129.4, 129.9 (t, *J* = 292 Hz), 132.3, 132.8, 135.6, 135.7, 136.7, 200.0; HRMS (EI) calcd for $C_{12}H_{13}OF_2Cl$ $[M + H]^+$ 246.0623, found 246.0616. Anal. Calcd for $C_{12}H_{13}OF_2Cl$: C, 58.43; H, 5.31. Found: C, 58.16; H, 5.32.

4-Chloro-1-(4-methoxyphenyl)-4,4-difluorobutan-1-one (2e): solid, mp, 40.5–43 °C, 13% and 9% yield, respectively, when using 1 or 5 equiv of anisole; ^{1}H NMR δ 2.77 (m, 2H), 3.25 (t, *J* = 7.5 Hz, 2H), 3.88 (s, 3H), 6.95 (dm, *J* = 9 Hz, 2H), 7.96 (dm, *J* = 9 Hz, 2H); ^{19}F NMR δ −51.4 (t, *J* = 12.4 Hz, 2F); ^{13}C NMR δ 32.3, 36.6 (t, *J* = 18.5 Hz), 55.7, 114.1, 129.4, 130.0 (t, *J* = 291 Hz), 130.5, 164.1, 195.1; HRMS (EI) calcd for $C_{11}H_{11}O_2F_2Cl$ $[M + H]^+$ 249.0494, found 249.0473. Anal. Calcd for $C_{11}H_{11}O_2F_2Cl$: C, 53.13; H, 4.46. Found: C, 53.50; H, 4.33.

(2,2-Difluorocyclopropyl)(4-methoxyphenyl)methanone (3e):[3] liquid, 39% and 51% yields, respectively, when using 1 or 5 equiv of anisole; ^{1}H NMR δ 1.68 (m, 1H), 2.30 (m, 1H), 3.36 (m, 1H), 3.72 (s, 3H), 6.96 (m, 2H), 7.54 (m, 2H); ^{19}F NMR δ −124.74 (m, 1F), −140.8 (m, 1F).

4-Chloro-4,4-difluoro-1-(thiophen-2-yl)butan-1-one (2f): liquid, 2% yield; ^{1}H NMR δ 2.79 (m, 2H), 3.30 (m, 2H), 7.00 (t, *J* = 4.5 Hz, 1H), 7.16 (dd, *J* = 5.7 and 1.2 Hz, 1H), 7.21 (dd, *J* = 3.8 and 1.0 Hz, 1H); ^{19}F NMR δ −51.5 (t, *J* = 12.4 Hz).

(2,2-Difluorocyclopropyl)(thiophen-2-yl)methanone (3f): solid, mp 47–49 °C, 84% yield; ^{1}H NMR δ 1.83 (m, 1H), 2.39 (m, 1H), 3.29 (m, 1H), 7.19 (t, *J* = 4.5 Hz, 1H), 7.72 (dd, *J* = 5.7 and 1.2 Hz, 1H), 7.82 (dd, *J* = 3.8 and 1.0 Hz, 1H); ^{13}C NMR δ 16.2 (t, 9 Hz), 30.2 (t, *J* = 11 Hz), 111.7 (t, *J* = 289 Hz), 128.7, 133.2, 135.0, 144.4, 183.2; ^{19}F NMR, δ - 124.6 (dtd *J* = 149,12.4 and 6.2 Hz, 1F), −140.9 (ddd, *J* = 148, 21, and 4.2 Hz, 1F); HRMS (EI) calcd for $C_8H_6OF_2S$ $[M + H]^+$ 189.0180, found 189.0190. Anal. Calcd for $C_8H_6OF_2S$: C, 51.06; H, 3.21. Found: C, 50.94; H, 3.11.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** ^{1}H, ^{13}C, and ^{19}F NMR spectra of compounds **2a**–**e** and **3f** and ^{1}H and ^{19}F NMR spectra of compounds **1**, **2f**, **3a**, **3b**, and **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wrd@chem.ufl.edu.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 7 and related text have been corrected as has an in-text reference to Scheme 9. The correct version reposted on April 14, 2011.